Nonvascular Needle and Shunt Placements for Fetal Therapy

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The nonvascular placement of needles and shunts for the in utero treatment of fetuses with fluid-filled, space-occupying anomalies has been done for about 10 years. The rationale for this approach is to attempt to prevent progressive impairment of organ function or lethal damage by early decompression. Experience has taught us that the key to success in these cases is the exclusion of associated anomalies and the use of appropriate tests to assess the residual organ function at the time of first diagnosis. In fetuses with hydrothorax, shunts can prevent pulmonary hypoplasia, and in those with obstructive uropathy, they can prevent the development of progressive lung hypoplasia and renal damage before a fetus is fully viable. In fetuses with ovarian cysts, prenatal puncture is occasionally indicated, but in those with hydrocephalus, the beneficial effect of prenatal drainage is more controversial. The catheters used for in utero placement have been improved and carry a smaller risk than open fetal surgical procedures.

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In 1985 Golbus of the University of California, San Francisco, one of the pioneers of fetal therapy, wrote as the guest editor of *Seminars in Perinatology* the following[1(p51)]:

In utero fetal therapy remains an experimental form of fetal medicine. Thus, it is very important that these approaches to in utero evaluation and management not be applied to the general care of obstetric patients. Fetal therapy should only be offered in centers where ongoing research is being done and where the multidisciplinary team approach to these problems is available.

This concept is still true almost ten years later, particularly in the area of nonvascular needle and shunt placement for in utero treatment. The percutaneous placement of umbilical needles for prenatal diagnosis and therapy is covered elsewhere in this issue.* This contribution, therefore, deals only with the in utero treatment of obstructive uropathy, hydrothorax, hydrocephalus, and ovarian cysts.

In a recent review we summarized the general questions that have to be addressed before contemplating any needle or shunt placement in utero[2]:

- What is the natural outcome of this anomaly? Will additional or irreversible damage be caused to the fetus if repair procedures are delayed until after birth?
- Is it possible to correct the anomaly or its consequences in utero? Will the procedure change the natural outcome?
- What is the risk to the mother and the fetus?

Surgical intervention in utero should be considered only if the natural history of the anomaly is frequently associated with neonatal severe handicap or early death; there is evidence (from animal models) that the natural history can be changed by the surgical procedure; and the risk to the mother is relatively small, as proved in a rigorous study of animals (such as nonhuman primates).

Intrauterine Obstructive Uropathy

The widespread use of modern grey-scale ultrasonography in obstetrics has permitted the recognition of obstructive uropathies more frequently and earlier in pregnancy than previously possible. Obstructive uropathies must be differentiated from a variety of mainly cystic congenital disorders of the fetus. Several reports have addressed the poor prognosis of fetuses with persistent urinary obstruction, particularly with oligohydramnios and resultant pulmonary hypoplasia.[3,4] The prognosis for fetuses with persistent obstruction is poor because the back-up of urine can both destroy the renal parenchyma and impede pulmonary development.[5,6] Retrograde pressure forms behind the obstruction and causes increasing dilation of the urinary system.[3] As documented in studies of animals, hydronephrotic and, perhaps, dysplastic changes occur in the renal parenchyma.[7] The severe oligohydramnios associated with bilateral urinary tract obstruction can

*See K. J. Moise, Jr, MD, "Intrauterine Transfusion With Red Cells and Platelets," on pages 318-324.

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result in pressure deformities of the face and limbs and pulmonary hypoplasia, the so-called Potter sequence. Neonatal death is often caused by respiratory tract insufficiency. The timing and the degree of obstruction are crucial determinants in the development of irreversible renal and pulmonary damage.[7-9]

Several indices have been used in the prenatal evaluation of renal function in fetuses with obstructive uropathy, including the amniotic fluid volume, the ultrasonographic appearance of the kidneys, and the biochemical composition of the fetal urine. In cases of severe urethral obstruction, the bladder can be profoundly distended (Figure 1), often associated with enlarged renal pelvises. Because sonography is especially accurate for detecting fluid-filled abnormal lesions, fetal urinary tract obstruction can easily be detected prenatally.[10] In cases of fetal urethral obstruction, the characteristic sonographic finding is the dilation of both the fetal urinary tract and the proximal urethra, resulting in a "keyhole" appearance,[11,12] usually in a male fetus. Even in cases of urethral or bladder outlet

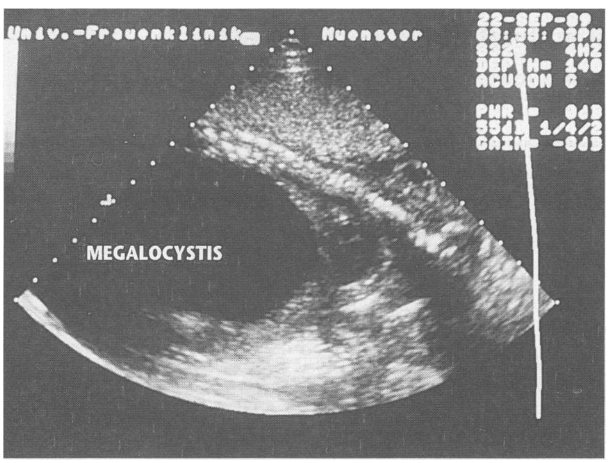

Figure 1.—The ultrasonogram shows a fetus with urethral obstruction and a grossly distended bladder (megalocystis) pushing the diaphragm upwards.

obstruction where a symmetric back-up pressure might be expected with uniform degrees of hydronephrosis in both kidneys, there is often considerable asymmetry in the degree of hydronephrosis of the kidneys.

Megalocystis and hydronephrosis as the first signs of obstructive uropathy can develop early in pregnancy, and they can be associated late in the first or early in the second trimester with severe oligohydramnios, but also with normal amounts of amniotic fluid. Wladimiroff and coworkers pointed out, however, on the basis of findings of weekly ultrasonograms in one patient, that slight bilateral hydronephrosis as a first sign of obstructive uropathy due to urethral valves could not be established before 30 weeks' gestation, although anuria developed and bilateral ureterocutaneostomy had to be carried out postnatally.[13] On the other hand, cases of transient in utero hydronephrosis have also been reported,[14,15] some of which possibly being due to fetal vesicoureteral reflux resolving in the course of maturation.

Besides urethral obstructions, ureteropelvic junction obstruction is the most common cause of hydronephrosis in neonates and children.[16] These cases can be differentiated prenatally because hydronephrosis is not associated with megalocystis as opposed to urethral obstruction.

It is difficult to quantify prenatally the degree of hydronephrosis. To facilitate communication and comparison of results in the literature, Grignon and associates proposed a morphologic classification of in utero urinary tract dilation.[17] They suggested that grade 1 dilation (anteroposterior diameter of the renal pelvis less than 10 mm) should be considered normal, whereas grades 2 and 3 with intermediate hydronephrosis require postnatal urologic surgical therapy in nearly half the cases. Grade 4, moderate dilation of the calyces with easily identified residual renal cortex, and grade 5, severe dilation of the calyces with atrophic cortex, were clearly considered serious disorders requiring a neonatal corrective operation. This classification may be helpful for communication, but because of the variability of the clinical course of fetal obstructive uropathies, any classification scheme is problematic.

For practical purposes, the systematic evaluation of fetal obstructive uropathies by Filly and colleagues provided valuable information—that cortical cysts had a sensitivity of 44% and a specificity of 100% in predicting renal dysplasia, whereas increased echogenicity had a sensitivity of only 57% and a specificity of 89%.[18,19] The severity of hydronephrosis was least predictive, with a sensitivity of 35% and a specificity of 78%. Therefore, the power of ultrasonography to assess the degree of renal residual function after the prenatal detection of bilateral hydronephrosis is still limited, even with the use of the best machines with high resolution.

Neither does the degree of dilation of the ureters correlate well with the degree of renal damage.[20] We share the experience of the Fetal Treatment Program in San Francisco that fetal kidneys that are obstructed severely enough to result in rupture of the collecting system and the formation of a perinephric urinoma and urinary ascites are unlikely to have adequate residual renal function.[21]

It remains to be investigated systematically whether the use of Doppler studies on the renal artery flow, which is now greatly aided by the introduction of color-coded Doppler sonography, can be helpful for the much-needed improvement of the prenatal assessment of kidney function in urinary tract obstruction. The hypothesis regarding the Doppler evaluation of the renal artery flow is that an increased resistance index correlates with the degree of parenchymal compression and subsequently with the degree of renal insufficiency.

Assessment of Fetal Renal Function In Utero

Because in cases with sonographically recognized obstructive uropathies ultrasonography cannot identify all dysplastic kidneys, biochemical studies from fetal urine specimens were done by the San Francisco Fetal Treatment Group.[19] Fetal urine is known to be produced from the 13th week of gestation onwards and is an ultrafiltrate of fetal serum made hypotonic by selective tubular absorption of sodium and chloride. In addition to this, it has been determined that the normal levels of sodium and chloride fall throughout gestation.[22] For example, a sodium level of 120 mmol per liter in fetal urine is still in the normal range at 15 weeks but clearly abnormal after 20 weeks' gestation.

In a retrospective analysis of fetal urine specimens in San Francisco, it was found that fetuses with hypotonic urine had later been found to have good renal function as opposed to those with isotonic urine, who later had poor renal function. Urine osmolarity had a similar predictive value. In summary, the San Francisco retrospective study revealed that urinary sodium levels above 100 mmol per liter, chloride levels above 90 mmol per liter, and osmolarity above 210 mOsm were associated with insufficient tubular reabsorption capacity and irreversibly damaged renal function at birth.

Lenz and co-workers showed that, as with plasma values, concentrations of neutral amnio acids in the fetal urine are also predictive of irreversibly destroyed kidneys because they reflect poor tubular capacity.[23] Later Nicolini and associates pointed out that the selection of fetuses for vesicoamniotic shunting can be further improved by serial sampling of each kidney separately.[24]

Like others,[25,26] however, we found that these useful variables are not always able to correctly select those cases in which drainage of the obstructed urinary tract might be beneficial. We therefore looked for additional determinants to improve the prenatal prediction about the renal function.[27]

In the postnatal and the prenatal periods, proteinuria in the course of renal disease is caused either by a disease process in the glomeruli or by damage in the tubular reabsorption capacity. Because this pathogenetic difference is expressed by the molecular weight of the proteins,[28] the site and degree of the underlying lesions in kidneys with pathologic proteinuria can be identified by separating urinary proteins on polyacrylamide gel electrophoresis with sodium dodecyl sulfate as detergent (SDS-PAGE). Molecules between 10 and 200×10^3 daltons can be separated and stained with Amidoblack by this technique. An increase in micromolecular proteins (molecular weight < 70,000) is indicative of an impairment in tubular reabsorption of those proteins that normally pass almost freely through the glomeruli.[29] The SDS-PAGE method not only separates proteins according to their molecular weight, but also allows their quantity to be estimated. In normal pregnancies at 18 weeks, no proteins other than albumin are found in fetal urine (Figure 2).

Using this new test we reported the successful shunting of a fetus with megalocystis and associated anhydramnios at 19 weeks' gestation in which urinary electrolytes and osmolarity were compatible with severe renal damage. Adding protein analysis by SDS-PAGE supported the prediction of a good outcome after shunt treatment and subsequent delivery at 36 weeks' gestation.[30]

Figure 2.—A fetal urine specimen obtained at 19 weeks' gestation was analyzed using polyacrylamide gel electrophoresis with sodium dodecyl sulfate. The fat band in the upper part of the panel represents albumin. Severe tubular damage is indicated by the presence of microprotein bands in the lower half of the gel.

Subsequently we used the SDS-PAGE method in utero, together with the San Francisco profile (modified for gestational age) in a series of 21 cases.[31] We found in this group of patients that the electrolyte and osmolarity evaluations were incorrect in four instances, whereas the SDS-PAGE results were in agreement with the ultimate outcome of the pregnancy in all of these cases. We therefore suggest that the SDS-PAGE evaluation should be added to previously described fetal urinary function tests in cases of severe and progressive urinary tract obstructions before decisions about the prenatal management are made.

In utero treatment should be reserved for fetuses with bilateral urinary tract obstruction, maintained renal function, decreased amniotic fluid volume, and no other life-threatening anomalies. Cytogenetic anomalies and congenital malformations of other systems are diagnosed in 15% to 40% of cases of fetal obstructive uropathy. The evaluation should include the karyotype (by amniocentesis, placental biopsy, or cordocentesis), echocardiography, and a detailed ultrasound examination to assess renal size or dysplastic changes and to evaluate fetal bladder filling.[9] The patterns of chromosomal abnormalities were related to the different types of renal defects. In mild hydronephrosis, the most common chromosome abnormality was trisomy 21, whereas in moderate to severe hydronephrosis, multicystic kidneys, or renal agenesis, the most common abnormalities were trisomies 18 and 13. If fetal visualization is impaired by severe oligohydramnios, the artificial installation of fluid will improve sonographic visibility. The observation of fetal behavior (drinking, filling of stomach and bladder) makes the study of fetal anatomy more accurate.

Most procedures of vesicoamniotic shunt placement have been done percutaneously with ultrasonographic guidance.[9] A double-coiled nylon catheter has been used in most cases, with good results. One-way valve catheters are not necessary because the pressure in the obstructed bladder usually exceeds that in the amniotic fluid, and there are adverse consequences if amniotic fluid goes into the bladder.

The fetal surgery registry coordinated by Frank Manning, MD, of the University of Manitoba, Canada, lists 98 cases as of March 1993 treated by indwelling shunts.[2] The longest follow-up is more than 11 years, and the overall survival has been 41%. Particularly at the beginning of the series, a number of patients were inappropriately chosen for surgical therapy, which considerably lowered the survival statistics. For example, several fetuses had a shunt placed before a chromosome abnormality was elucidated. When appropriately stratified by cause, survival reaches as much as 70% for male fetuses with a posterior urethral valve.

Shunt Procedures

The transabdominal percutaneous intrauterine placing of a suprapubic bladder shunt is currently mainly done by using a Rocket shunt technique as developed by Rodeck (Figure 3).[32] After a directional approach has been chosen, the maternal skin is prepared, and a scalpel blade is used to nick the maternal skin. The shunt loader is then inserted into the uterine cavity and suprapubically into the fetal bladder. After this the trocar is removed. A plastic double pigtailed catheter with a central wire stylet is inserted the entire length of the catheter. The wire stylet is then removed. A short plunger is used to push the distal half of the catheter into the fetal bladder. A long plunger is inserted down the shaft to touch the proximal end of the catheter. The outer tube is then pulled back while holding the plunger steady, resulting in the proximal half of the catheter being dropped into the amniotic cavity.

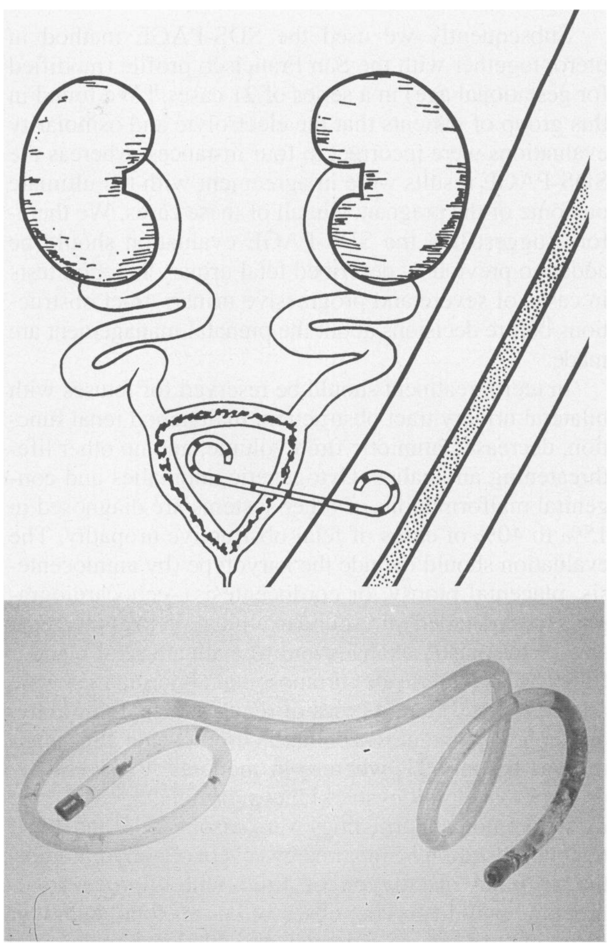

Figure 3.—A vesicoamniotic catheter is used in fetal obstructive uropathy. **Top,** A schematic depicts the in utero placement of the catheter in the fetal bladder. **Bottom,** The Rodeck shunt is shown after postnatal removal from an infant who had the shunt placed in utero.

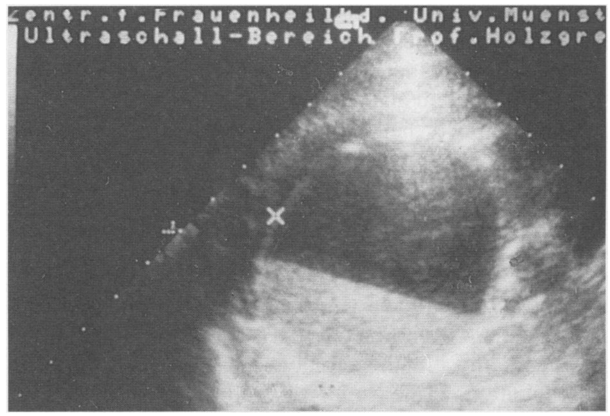

Figure 4.—The sonogram shows the typical appearance of fetal ovarian cysts with sedimented cells in the lower part of the cysts.

Patients who have undergone successful shunting procedures are a testimonial to the possible benefit of early, aggressive evaluation of fetal renal function and for successful fetal treatment in a few selected cases of obstructive uropathies.

With more advanced ultrasonograms and biochemical tests, it is obvious that most of the initial early attempts at fetal urinary diversion were performed on poorly chosen patients. We now need to start afresh in creating a data base to evaluate the natural history, function, and possibilities for intervention by vesicoamniotic shunt placement.

Management of Fetal Ovarian Cysts In Utero

Although it is known from autopsy specimens of stillbirths and neonates that small follicular cysts are not unusual in full-term infants, large cysts are only rarely noted clinically or by sonography.[33] The diagnosis can be suspected prenatally if a cystic lesion is visualized next to a kidney in a female fetus (Figure 4). Prenatally these cysts are usually uncomplicated and often disappear spontaneously after delivery, but sometimes they require surgical intervention because of their size or secondary complications.[34,35] If they are taken out by laparotomy in the neonatal period it is difficult even with microsurgery not to harm the small ovary, which is often intimately integrated into the wall of the cyst. It therefore seems prudent either to allow even large cysts to regress spontaneously or to decompress those that are causing complications.

From our own experience with 13 such cases, we know that complications can occur prenatally from tor-

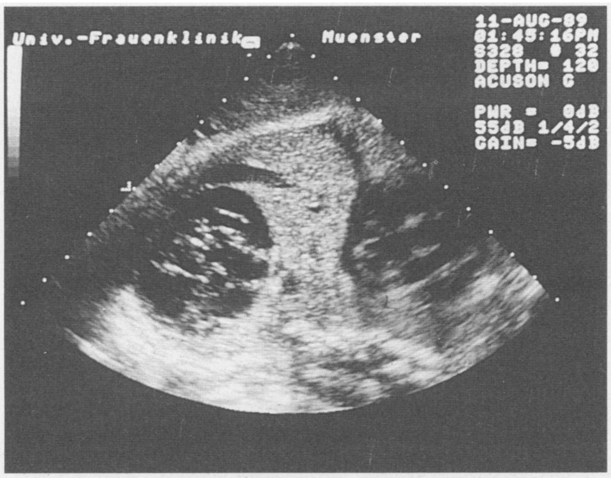

Figure 5.—In utero torsion of a fetal ovarian cyst is seen on the sonogram, which shows the inhomogeneous internal structure.

sion of the pedicle and subsequent necrosis or hemorrhage into the cyst (Figure 5). Therefore, we recommend prenatal decompression especially if the cyst is large and is a "wandering mass."

High levels of prostaglandin E_2, progesterone, and testosterone in the cystic fluid confirm the diagnosis after prenatal puncture. The differential diagnosis includes choledochal,[36] paranephric, sacrococcygeal, mesenteric, and urachal cysts. The precise topography aided by color-coded Doppler mapping of the vasculature can be helpful in the differential diagnosis.

In summary, the general approach to fetal ovarian cysts in utero is conservative, but in special cases prenatal decompression seems useful for improving the outcome.

Management of Ventriculomegaly In Utero

In the early 1980s much of the focus regarding the potential for fetal therapy centered on obstructive ventriculomegaly. Interest in this disorder emerged from the relative ease of diagnosis by ultrasonography and was amplified by the success rates of shunting procedures performed in neonates. The concept, as developed in animal models, was that early shunting of ventriculomegaly in utero might prevent the irreversible damage caused by prolonged increased intracranial pressure. The original ventriculoamniotic shunt for prenatal placement was developed about ten years ago by Clewell and co-workers in Denver, Colorado, and also applied first by this group in utero.[37]

In humans the experience with ventriculoamniotic shunts seems at first glance to be disappointing. As of July 1993, less than 50 cases of fetal ventriculomegaly treated in utero by ventriculoamniotic shunts were reported to the International Fetal Registry.[38] In most instances, the shunting was performed in fetuses presumed to have ventriculomegaly or hydrocephalus due to aqueductal stenosis. The mean gestational age at diagnosis was 25 ± 2.73 weeks (range, 18 to 31), and the mean age at treatment was 27 ± 2.6 weeks (range, 23 to 33). The duration of effective therapy cannot be determined from registry data because objective means for assessing shunt function are not available. Of 41 fetuses with hydrocephalus treated by ventriculoamniotic shunting, 34 survived. Of the 7 deaths that occurred, 4 could be directly attributed to trauma at the time of the shunt placement or to premature labor occurring within 48 hours of shunt placement. Thus, the crude mortality rate for the procedure is about 9%. The 34 surviving infants have been observed on average for 12.2 ± 5.8 months (range, 6 to 36). Of these, 14, all with aqueductal stenosis, are thus far reported as normal at follow-up evaluation. The remaining survivors all showed varying degrees of neurologic handicap, and most of the children (18 of 34 survivors, 53%) are classified as having severe handicaps. These infants all exhibit gross delay in reaching developmental milestones, and in infants, the tested developmental quotient was always less than 60. Five of these infants have cortical blindness, three have seizure disorders, and two have spastic diplegia. The outcome among survivors was related principally to the primary cause of obstructive hydrocephalus. Aqueductal stenosis of uncertain cause was the most common etiologic factor for obstructive hydrocephalus (28 of 41 cases, 68%), and the only intact survivors are found in this group.

The results of ventriculoamniotic shunting for fetal ventriculomegaly have been disappointing,[39] and consequently there has been a de facto moratorium in place since the early 1980s.[2] The hope of selecting fetuses who otherwise would be severely impaired by ventriculomegaly and of avoiding irreversible damage by intrauterine treatment was substituted in a few instances with the survival of severely affected infants who otherwise would have died. In addition to the poor outcomes in treated fetuses, abandonment of the concept of shunting for ventriculomegaly must be considered for several reasons.[40] Analysis of the cases of ventriculoamniotic shunt placement performed in the 1980s and reported in the registry shows that selection criteria were not always employed appropriately, and fetuses with ventriculomegaly associated with other severe anomalies (such as holoprosencephaly or autosomal trisomies) also were given the benefit of intrauterine treatment.

Our own experience and current reports demonstrate that the natural history of fetal ventriculomegaly is poor in general.[40] The major determinant of the prognosis was the association with other intracranial or extracranial malformations. Additional malformations affect 70% to 85% of fetuses with ventriculomegaly, and all such cases suffer perinatal mortality or severe morbidity. Even if a diligent search for additional malformations was performed by combining a detailed ultrasound study of the fetus with amniocentesis for karyotyping and amniotic fluid α-fetoprotein and acetylcholinesterase assessment, as much as 40% of abnormalities would not be detected, even by experienced personnel.

The apparently obvious candidates for in utero ventricular shunting are the fetuses with isolated progressive obstructive ventriculomegaly as opposed to asymmetric hydrocephalus due to primary brain malformation (Figure 6). The number of cases is limited by a high rate of associated anomalies and by the relative failure to exclude additional malformations prenatally. The severity of ventriculomegaly is not always predictive of outcome or even of the need for postnatal shunt, as ventriculomegaly may not be associated with elevated intracranial pressure.

Considering the uncertainty and the difficulty of an accurate prenatal diagnosis, the intrauterine treatment of fetal ventriculomegaly remains a controversial and highly experimental procedure that is currently moribund because of the moratorium. When the option in midtrimester, however, is between terminating the pregnancy or simply observing the progressive dilation of the ventricles, the placement of a ventriculoamniotic shunt should present a third option in selected cases. Given the few good candidates and the need to develop a new catheter (as none is currently available), a carefully designed study should be performed in one of the few centers experienced in the technical aspects of ventriculoamniotic shunt placement to settle the question of its usefulness.

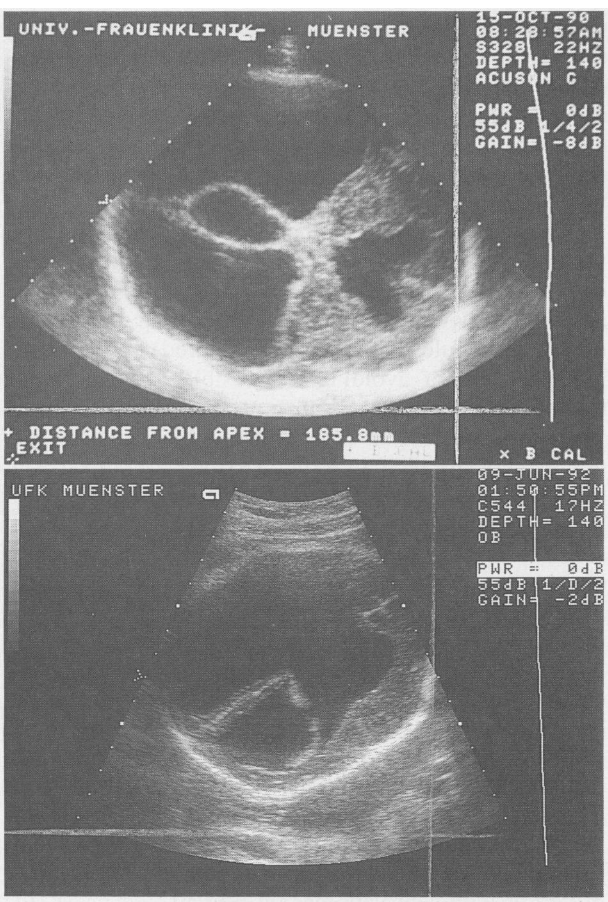

Figure 6.—Top, A symmetric type of hydrocephalus due to aqueductal stenosis is shown. **Bottom,** The sonogram shows the asymmetric type of hydrocephalus due to primary brain malformation.

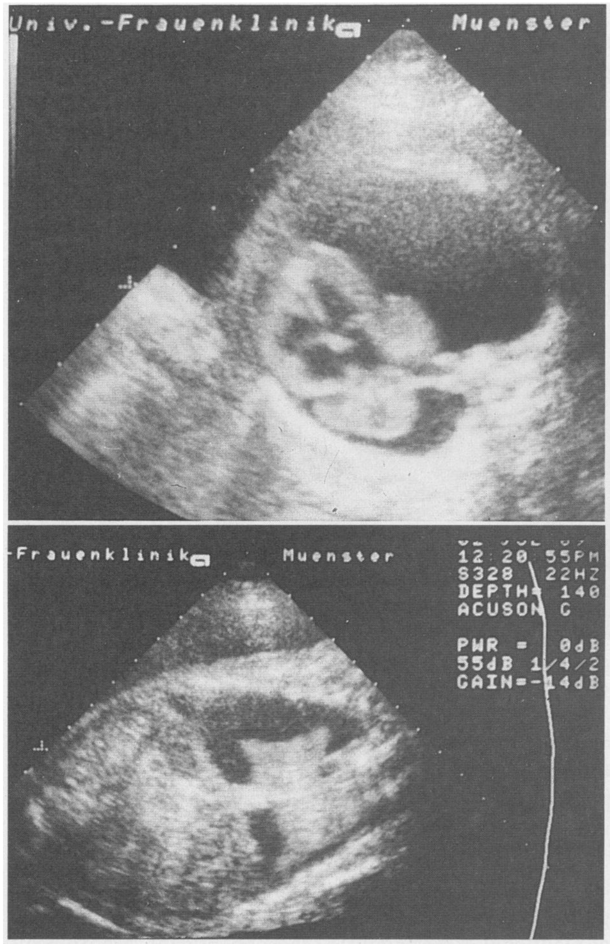

Figure 7.—The grey-scale sonograms reveal fetal hydrothorax: **top,** a transverse section; **bottom,** a longitudinal section.

Thoracoamniotic Shunting

Intrauterine mediastinal compression by conditions such as cystic adenomatoid malformation and pleural effusions can lead to the development of hydrops and polyhydramnios, which are associated with a high risk of premature delivery and intrauterine or neonatal demise.

Isolated pleural effusions (hydrothorax) in the fetus either may resolve spontaneously or may be treated effectively after birth. In some cases, however, severe and chronic compression of the fetal lungs in utero can result in pulmonary hypoplasia and neonatal death. In others, mediastinal compression leads to the development of hydrops and polyhydramnios, which are associated with a high risk of premature delivery and perinatal death. Fetal hydrothorax can be visualized well in utero by grey-scale sonography (Figure 7).

The data from fetuses with isolated pleural or pericardial effusions suggest that certainly in some cases short-term decompression by thoracocentesis or temporary

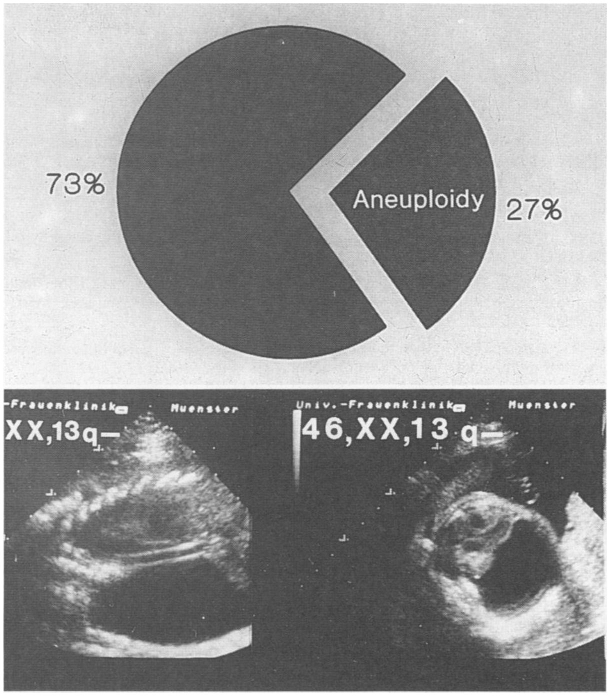

Figure 8.—Chromosomal disorders are shown in cases of fetal hydrothorax. **Top,** the rate of aneuploidies in a series of 22 cases is illustrated; 6 patients were affected. **Bottom,** The ultrasonograms are of fetuses with hydrothorax and a structural chromosomal abnormality.

drainage may disrupt the underlying disorder. In most cases, however, the fluid reaccumulates within 24 hours, requiring repeated procedures that are likely to be more traumatic than thoracoamniotic shunting.

The data collected by Nicolaides and associates indicate that thoracoamniotic shunting is useful for the diagnostic evaluation of fetuses with abnormal collections of intrathoracic fluid.[2] First, the diagnosis of an underlying cardiac abnormality or other intrathoracic lesion may become apparent only after effective decompression and return of the mediastinum to its normal position. It can also be useful in the prenatal diagnosis of pulmonary hypoplasia because in such cases, the lungs often fail to expand after shunting. Furthermore, it may help to distinguish between hydrops due to the primary accumulation of pleural effusions, in which the ascites and skin edema may resolve after shunting, and other causes of hydrops, such as infection, in which drainage of the effusions does not prevent worsening of the hydrops.

Thoracoamniotic shunting is also an effective and apparently safe method of the ongoing drainage of fetal pleural effusions or pulmonary cysts in utero. It can reverse fetal hydrops, resolve polyhydramnios and thereby reduce the risk of preterm delivery, and, most important, it may prevent pulmonary hypoplasia. The alternative management of pleural effusions by thoracocentesis immediately before or after delivery could prevent respiratory distress in the neonate if this is the result of simple mechanical compression of otherwise normally developed lungs. Such treatment would not prevent pulmonary hypoplasia due to prolonged intrathoracic compression or, indeed, progressive disease from pleural effusions to hydrops fetalis and intrauterine death. Moreover, in a proportion of hydropic fetuses, thoracoamniotic shunting does not prevent their death due to the underlying disease causing the hydrops. Similar to the other malformations discussed here, prenatal karyotyping also needs to be done before any in utero shunt placement, because the rate of aneuploidies and structural chromosomal anomalies (Figure 8) is high. Karyotyping often can be performed from lymphocytes out of the pleural effusion fluid after the initial percutaneous umbilical sampling.

In summary, whereas the percutaneous approach under ultrasonographic guidance seems to be the preferred method for placing a shunt in a hollow enlarged viscus, the correction of more extensive fetal anomalies such as diaphragmatic hernia or large adenomatoid lung malformation might require more extensive and more invasive operations on both mother and fetus ("open surgery").[41] With improved quality of the catheters for in utero placement and a lower risk of obstruction, displacement, and other complications, the significantly higher risk of open fetal operations needs even stronger justification. About ten years after the initial nonvascular shunt placement in utero by the San Francisco Fetal Treatment Group, worldwide experience has shown that surgical intervention is indicated only in a small group of carefully selected fetuses without lethal associated malformations but with progressive sequelae from isolated obstruction before viability.

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